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1: Cancer Res 2001 Aug 15;61(16):6012-9

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conceres.aacrjournals.org

A conditional replication-competent adenoviral vector, Ad-OC-E1a, to cotarget prostate cancer and bone stroma in an experimental model of androgen-independent prostate cancer bone metastasis.

Matsubara S, Wada Y, Gardner TA, Egawa M, Park MS, Hsieh CL, Zhou HE, Kao C, Kamidono S, Gillenwater JY, Chung LW.

Department of Urology, Molecular Urology and Therapeutics Program, University of Virginia School of Medicine, Charlottesville, Virginia 22908, USA.

Prostate cancer has a high propensity to metastasize to bone, which often resists hormone, radiation, and chemotherapies. Because of the reciprocal nature of the prostate cancer and bone stroma interaction, we designed a cotargeting strategy using a conditional replication-competent adenovirus to target the growth of tumor cells and their associated osteoblasts. The recombinant Ad-OC-E1a was constructed using a noncollagenous bone matrix protein osteocalcin (OC) promoter to drive the viral early E1a gene with restricted replication in cells that express OC transcriptional activity. Unlike Ad-PSE-E1a, Ad-OC-E1a was highly efficient in inhibiting the growth of PSA-producing (LNCaP, C4-2, and ARCaP) and nonproducing (PC-3 and DU145) human prostate cancer cell lines. This virus was also found to effectively inhibit the growth of human osteoblasts and human prostate stromal cells in vitro. Athymic mice bearing s.c. androgen receptor-negative and PSA-negative PC-3 xenografts responded to a single intratumoral administration of 2×10^9 plaque-forming unit(s) of Ad-OC-E1a. In SCID/bg mice, intraosseous growth of androgen receptor-positive and PSA-producing C4-2 xenografts responded markedly to i.v. administrations of a single dose of Ad-OC-E1a. One hundred percent of the treated mice responded to this systemic Ad-OC-E1a therapy with a decline of serum PSA to an undetectable level, and 80% of the mice with PSA rebound responded to the second dose of systemic Ad-OC-E1a. Forty percent of the mice were found to be cured by systemic Ad-OC-E1a without subsequent PSA rebound or tumor cells found in the skeleton. This cotargeting strategy shows a broader spectrum and appears to be more effective than systemic Ad-PSE-E1a in preclinical models of human prostate cancer skeletal metastasis.



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1: J Cell Sci 2001 Jun;114(Pt 11):2085-94

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Sonic hedgehog increases the commitment of pluripotent mesenchymal cells into the osteoblastic lineage and abolishes adipocytic differentiation.

Spinella-Jaegle S, Rawadi G, Kawai S, Gallea S, Faucheu C, Mollat P, Courtois B, Bergaud B, Ramez V, Blanchet AM, Adelmant G, Baron R, Roman-Roman S.

Bone Diseases Group, Department of Biotechnology, Hoechst-Marion-Roussel, 111 route de Noisy, 93230 Romainville, France.

The proteins of the hedgehog (Hh) family regulate various aspects of development. Recently, members of this family have been shown to regulate skeletal formation in vertebrates and to control both chondrocyte and osteoblast differentiation. In the present study, we analyzed the effect of Sonic hedgehog (Shh) on the osteoblastic and adipocytic commitment/differentiation.

Recombinant N-terminal Shh (N-Shh) significantly increased the percentage of both the pluripotent mesenchymal cell lines C3H10T1/2 and ST2 and calvaria cells responding to bone morphogenetic protein 2 (BMP-2), in terms of osteoblast commitment as assessed by measuring alkaline phosphatase (ALP) activity. This synergistic effect was mediated, at least partly, through the positive modulation of the transcriptional output of BMPs via Smad signaling. Furthermore, N-Shh was found to abolish adipocytic differentiation of C3H10T1/2 cells both in the presence or absence of BMP-2. A short treatment with N-Shh was sufficient to dramatically reduce the levels of the adipocytic-related transcription factors C/EBPalpha and PPARgamma in both C3H10T1/2 and calvaria cell cultures. Given the inverse relationship between marrow adipocytes and osteoblasts with aging, agonists of the Hh signaling pathway might constitute potential drugs for preventing and/or treating osteopenic disorders.

PMID: 11493644 [PubMed - in process]



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1: Bone 2001 Jul;29(1):54-61

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Characterization of human bone morphogenetic protein (BMP)-4 and -7 gene promoters: activation of BMP promoters by Gli, a sonic hedgehog mediator(1).

Kawai S, Sugiura T.

Laboratory for Bone Research, Discovery Research Laboratories, Hoechst Marion Roussel, Ltd., Kawagoe, Saitama, Japan

Among the bone morphogenetic protein (BMP) family, which plays a crucial role not only in bone formation but also in development, BMP-2, -4, and -7 participate predominantly in various aspects. To undertake complex tasks, their expression is strictly controlled. In this study we isolated and analyzed the 5'-flanking regions of the human BMP-4 and -7 genes to elucidate the mechanism of their temporally and spatially specific expression. As for BMP-4 expression, a reverse transcription-polymerase chain reaction (RT-PCR) assay with specially designed sets of primers demonstrated that osteoblastic SaOS-2 and Hos cells expressed two types of transcripts comprising one of the 5'-untranslated first exons, whereas MG63 cells displayed only the transcript with the BMP-4 proximal first exon. Likewise, RT-PCR revealed that Hos and MG63 cells expressed BMP-7. Subsequent 5'-RACE confirmed an alternative usage of the BMP-4 first exons with clustered multiple transcription start sites in the distal exon and the sole start site in the proximal exon. The transcription start site of the BMP-7 gene was found to be far upstream (764 bp) of the initiation ATG codon. We constructed a series of deletion mutants of fusions between these BMP promoters and the luciferase gene and examined their activity by transient transfection into osteoblastic Hos and renal COS-7 cells. The degree of distal and proximal BMP-4 promoter activity was in accordance with the expression level of the corresponding transcripts. Both distal and proximal BMP-4 promoters possessed suppressor elements that are operative only in Hos cells. The positive and negative elements identified in the BMP-7 promoter were more remarkably effective in Hos cells. The activities of the respective BMP-4 promoters and BMP-7 promoter were all stimulated upon the cotransfection of a potential sonic hedgehog (SHH) mediator, Gli1 or Gli3 into COS-7 cells, providing direct evidence that the Gli proteins are capable of inducing the BMP expression. Our systems are helpful for assessment of the complicated interactions of molecules involved in the skeletogenesis and developmental processes.